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Photodynamic Therapy: Enhancement of phthalocyanine targeting from modifications on the macrocycle to the use of protein delivery vehicles

By

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It is not what we know that is important,
it is what we do not know.

Charles F. Kettering

A task without a vision is drudgery.
A vision without a task is a dream.
A task with a vision is victory.

To Wesley,

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Abbreviations and Symbols

A549 cells	adenocarcinoma lung cancer cells
Ad2wt	wildtype adenovirus serotype 2
AlPcS	aluminum sulfophthalocyanine
$AlPcS_{2adj}$	aluminum disulfophthalocyanine
$AlPcS_4$	aluminum tetrasulfophthalocyanine
$AlPcS_4(C_n)$	aluminum mono-(alkylaminosulfonyl)-tetrasulfophthalocyanine
$AlPcS_4A_1$	aluminum mono(6-carboxypentylaminosulfonyl)tetrasulfophthalocyanine
$AlPcS_4A_2$	aluminum di(6-carboxypentylaminosulfonyl)tetrasulfophthalocyanine
B_{max}	receptor density
ATP	adenosine triphosphate
BPD	benzoporphyrin derivative
BSA	bovine serum albumin
CRM	Cremophor EL
DDM	aspartate-aspartate-methionine peptidic sequence
DMEM	Dulbecco's modified Eagle's medium
DMF	N,N-dimethylformamide
ECM	extracellular matrix
EDTA	ethylenediamine tetraacetic acid
EGF	epidermal growth factor
EMT-6 cells	murine mammary tumor cells
ε	epsilon, molar extinction coefficient
ERK	extracellular regulating kinase
FAK	focal adhesion kinase
FCS	fetal calf serum
HSA	human serum albumin
HEP-2 cells	human epidermoid laryngeal carcinoma
HpD	hematoporphyrin derivative
HPPI	3α-hydroperoxy-1,2,3,3α,8,8α-hexahydropyrrolo[2,3β]indole-2-carboxylic acid

IC	internal conversion
ISC	intersystem crossing
LDL	low-density lipoprotein
λ_{max}	maximum absorption wavelength
MOI	multiplicity of infection
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-(diphenyltetrazolium bromide)
O. D.	optical density
PAGE	polyacrylamide gel electrophoresis
PBS	phosphate-buffered saline
PDT	photodynamic therapy
PEG	polyethylene glycol
PFU	plaque forming unit
ϕ	quantum yield
PI-3 kinase	phosphatidylinositol 3-kinase
PLA	poly(D,L-lactic acid)
RGD	arginine-glycine-aspartic acid peptidic sequence
ROS	reactive oxygen species
R_t	retention time
S_0	ground state of sensitizer
S_1	singlet excited state of sensitizer
SDS	sodium dodecyl sulfate
$^1O_2$	singlet oxygen
Sens*	excited state of sensitizer
Sf9	*Spodoptera frugiperda*
τ_T	lifetime of triplet state of sensitizer
T_1	triplet excited state of sensitizer
TAE	Tris-acetate EDTA
TE	10 mM Tris pH 7.5, 1 mM EDTA
TFA	trifluoroacetic acid
TNF	tumor necrosis factor

Abstract- Photodynamic therapy is a promising treatment modality that involves the localization of a light-sensitive drug or photosensitizer in the target tissue prior to illumination with visible light. In the presence of molecular oxygen, cytotoxic agents are generated upon illumination and trigger a cascade of biochemical responses that may eradicate both malignant and non-malignant conditions. Phthalocyanine derivatives are second generation photosensitizers with enhanced photophysical, photochemical and photobiological properties as compared to the clinically accepted hematoporphyrin derivative Photofrin®. The current study aims at improving the targeting of these photosensitizers to cancerous tissues either through modifications on the phthalocyanine macrocycle or through protein carriers. $AlPcS_4$ derivatives substituted with long aliphatic chains of varying lengths were photodynamically active *in vitro* against a lung adenocarcinoma cell line, A549 cells. Activity varied directly with the degree of lipophilicity: $AlPcS_4$(C16) > $AlPcS_4$(C12) > $AlPcS_4$(C8) > $AlPcS_4$(C4). *In vivo* studies using the EMT-6 murine model were promising, requiring 0.2 μmol kg^{-1} and 400 J cm^{-2} to completely ablate the tumor. LDL receptor expression is often upregulated in cancer cell membranes. Therefore, in order to enhance Pc targeting, LDL was loaded with AlPcS by two different approaches. The $AlPcS_4$(C12) derivative was non-covalently inserted in the phospholipid bilayer of LDL particles. Conversely, $AlPcS_4$ substituted with two caproic acid spacer chains were covalently attached to the LDL protein moiety. While the latter had only marginal success, the former proved to be photodynamically active both *in vitro* and *in vivo*. To further exploit cell surface receptors as potential targets in PDT, adeno-viral proteins were covalently labeled with $AlPcS_4$. Adenoviruses penetrate the cell via receptor mediated endocytosis. The Ad penton base contains 5 repeats of the peptidic RGD binding sequence. This motif binds with high affinity to several members of the integrin receptor family. Integrin receptors play a major role in tumorigenesis and metastases with altered expression being a factor. The class of integrin receptors with high affinity for the RGD sequence is expressed in high numbers on A549 cells. Cell uptake of the $AlPcS_4$-adenovirus protein conjugates was enhanced over the parental Pc; however, photocytotoxicity results were unfavorable. *In vivo* studies using the same rodent model as that of the LDL study were encouraging. The $AlPcS_4$-adenovirus protein conjugates caused complete tumor regression at a dose of 0.5

μmol kg^{-1} and 400 J cm^{-2}. The role of RGD on PDT induced cell death was also investigated. It was anticipated that soluble RGD would have a synergistic effect on PDT induced apoptosis yet the opposite was found. RGD enhanced cell survival following PDT in a dose dependent manner in both a receptor negative (EMT-6) and a receptor positive (A549) cell line. This was an unexpected phenomenon and warrants further investigation. Once understood, the possibility of designing peptidic carriers for photosensitizers or adjunct therapies using the RGD peptide are within the realm of possibility. Nonetheless, specific targeting of $AlPcS_4$ derivatives to cancer cells resulted in enhanced photodynamic activity as compared to the parental molecule, $AlPcS_4$.

Chapter 1.

Introduction

1. Introduction

Cancer is one of the leading causes of death and disease in the Western World. Over 1.2 million new cases of cancer were diagnosed in the United States in 1999 (American Cancer Society) while approximately one third of the population of Western Europe can expect to be touched by the disease within their lifetime (Brown et al., 1999). Cancer is an unregulated proliferation of transformed cells displaying an altered phenotype, distorted differentiation and genetic instability. These cells usually spread to and infiltrate distant sites of the body, giving rise to metastases (Fingert et al, 1997). Traditional cancer treatment modalities such as surgery, chemotherapy and radiation therapy aim at locoregional or systemic control of the malignancy and involve a delicate balance between removing or destroying diseased tissue while sparing neighboring healthy cells. These conventional therapies produce serious side effects caused by the loss of normal cell function as a result of their relatively indiscriminate cytotoxic effects. Furthermore, despite operating at near optimal efficiencies, these treatment protocols often are not sufficiently effective, frequently leading to important recurrences. While therapeutic improvements are continually being made, there have been no substantial enhancements in survival for a number of major malignancies over the past decade (Brown et al., 1999). Consequently, the search for new and improved treatment protocols that exhibit more selectivity for diseased tissue and less morbidity remains unabated.

Photodynamic therapy (PDT) is a promising new treatment modality that has recently been accepted in clinic as a curative and/or palliative therapy for cancer and also for non-malignant disorders. Photodynamic therapy entails a classic binary system which combines a light-activated drug (photosensitizer) with light of the appropriate wavelength

that is consistent with the absorption spectrum of the given photosensitizer. Illumination of the photosensitizer typically with visible light triggers a sequence of photophysical, photochemical and photobiological processes that cause irreversible photodamage to the target tissue. Neither the photosensitizer nor the light are harmful by themselves and only produce cytotoxic species when combined in the presence of molecular oxygen. Like all new cancer therapies, PDT primarily aims at destroying diseased tissue without causing inordinate injury to surrounding healthy cells. This targeting of diseased tissue is aided by a number of factors unique to PDT. The dual selectivity of PDT is produced by both a preferential uptake and/or prolonged retention of the photosensitizer by the diseased tissue along with the ability to confine activation of the photosensitizer to the target volume. This is accomplished by restricting the illumination to that specific volume, often using lasers and fiber optics. Hence, PDT allows for the selective destruction of tumors, providing the potential for minimal morbidity and large therapeutic indices.

1.1 Historical perspective

The therapeutic benefits of light have been known since the ancient world with early Greek, Egyptian, Roman and Indian civilizations all recognizing the healing powers of the sun. In India, as early as 1400 B.C., extracts of *Psoralea corylifolia* were given orally, followed by exposure to sunlight, in order to treat vitiligo (Daniell and Hill, 1991; Bonnett, 1999). Modern photodynamic therapy however can trace its origins to the beginning of the 20th century when a medical student, Oscar Raab, working under the direction of Dr. von Tappeiner in Munich, noticed the lethal effects of light on *Paramecia* treated with acridine dyes (Raab, 1900). This phenomenon was more extensively studied

by von Tappeiner and Jodlbauer who coined the term "photodynamic action" (von Tappeiner and Jodlbauer, 1907). It was noted that other compounds such as eosin were able to induce rapid cell kill in the presence of light. It was established that dissolved molecular oxygen is needed for the reaction to occur. The first attempt at using PDT as a cancer treatment dates to 1903 where topically applied eosin was used in conjunction with sunlight to treat skin cancer (von Tappeiner and Jesionek, 1903). The relative specificity of PDT was clearly demonstrated by Lipson in 1961 when the use of hematoporphyrin derivative (HpD) for the fluorescent detection of tumor tissue was reported (Lipson et al., 1961). In 1975, Dougherty first reported the eradication of transplanted animal tumors with HpD and red light without excessive damage to surrounding skin (Dougherty et al., 1975). This was soon followed by the first systemic clinical trials in humans and since then the field of PDT has rapidly expanded (Dougherty et al., 1978). Due to the clinical acceptance of Photofrin®, verteporfin and the prodrug 5-aminolaevulinic acid (ALA), PDT has evolved into a useful treatment modality.

1.2 Mechanisms of photosensitization

Upon illumination, the photosensitizer is excited from its electronic ground state (S_0) to its first excited state (S_1). This excited singlet state has a lifetime in the nanosecond range (Phillips, 1997), which is far too short for effective interaction with surrounding biological molecules. The S_1 state can dissipate its excitation energy via radiative fluorescence or non-radiative internal conversion (IC). The most important of these processes in terms of PDT, however, is intersystem crossing (ISC) to the first excited triple state (T_1) with the corresponding change in electron spin. The lifetime of the T_1 state is typically in the μs to ms range since the return $T_1 \rightarrow S_0$ is spin-forbidden

(Ochsner, 1997). The large increase in lifetime allows for the excited photosensitizer to interact with its environment and it is generally accepted that the triplet state is responsible for the generation of the cytotoxic species produced during PDT in the majority of cases (Sharman et al., 2000).

This excited triplet state can interact in one of two ways, defined as Type I and Type II (Figure 1). The T_1 state of the excited photosensitizer can be quenched via a hydrogen atom extraction or an electron transfer reaction with neighboring substrates. These reactions termed a Type I mechanism, lead to the formation of radicals and radical ions. These radical species react efficiently with molecular oxygen, leading to important oxidative damage and the production of reactive oxygen species such as superoxide anion, hydrogen peroxide and the hydroxyl radical. The following radical chain reactions cause important biological lesions. On the other hand, the T_1 state can transfer its energy to molecular oxygen via a triplet-triplet annihilation reaction, generating singlet oxygen (Sharman et al., 2000). This Type II reaction mechanism has been shown to be predominant during PDT. Singlet oxygen, the most important cytotoxic agent generated during PDT, is highly reactive due to its zwitterionic character and can readily react with a number of biologically important substrates including amino acids, phospholipids, and nucleic acids (Singh, 1982). This leads to disruption of cellular and mitochondrial membranes, increased cellular permeability, the loss of vital protein and enzyme function and irreparable DNA damage, all of which can be lethal to the cell. It is generally accepted that the Type II mechanism prevails during PDT and that singlet oxygen is the most important cytotoxic species produced (Sharman et al., 2000; Weishaupt et al., 1976; Valenzeno, 1987; Fuchs and Thiele, 1998). The range of singlet oxygen in cellular

medium is limited to approximately 45 nm (Moan and Boye, 1981 and Moan, 1990). With the diameter of human cells ranging from 10^4 to 10^5 nm, the site of primary generation of singlet oxygen consequently determines which subcellular target is attacked, either initiating an apoptotic or necrotic response. Appendix I outlines the importance of singlet oxygen in photodynamic therapy. However, while it is known that Type II processes predominate during PDT, Type I mechanisms become important at low oxygen concentrations and in more polar environments (Ochsner, 1997; Sharman et al., 2000). These Type I mechanisms are no doubt involved in most photodynamic processes to a certain degree. Irrespective of the initial reaction, both Type I and Type II mechanisms lead to similar oxidative damage and comparable free radical chain reactions. The two processes, Type I and Type II are outlined in figure 1.

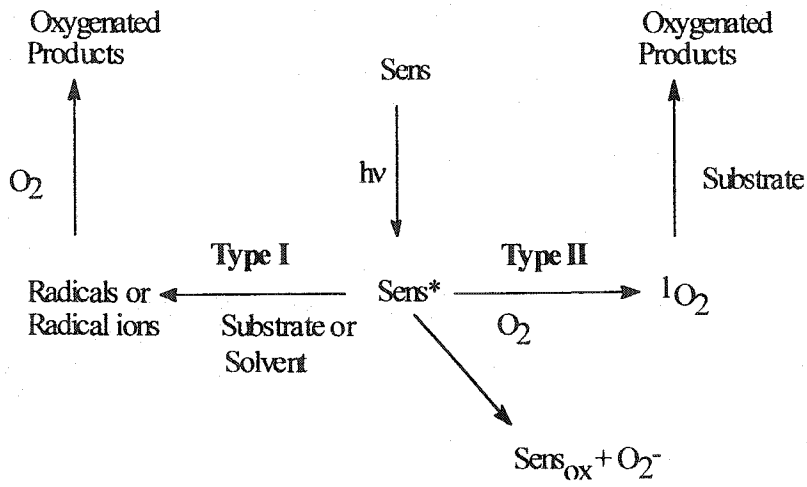

Figure 1. Diagramatic presentation of Type I and Type II photosensitized oxidation reactions (Adapted from C. S. Foote, 1991)

1.3 First generation photosensitizer: Hematoporphyrin derivative

The first photosensitizers accepted for clinical use by governmental regulatory agencies are the first generation hematoporphyrin derivatives such as Photofrin®.

Photofrin®, an enriched sample of the more active dimeric and oligomeric components, has been accepted in several countries for the treatment of early- and late-stage lung cancer, superficial and advanced oesophageal cancer, bladder cancer, superficial and early-stage gastric cancer, early stage cervical cancer and cervical dysplasia. In addition, Photofrin® is being investigated as a possible therapy for a number of other malignant and non-malignant conditions. Other hematoporphyrin derivatives are also being used, with Photoheme accepted for clinical use in Russia for easily accessible cancers including skin, breast, oropharyngeal, lung, larynx and gastrointestinal cancers along with psoriasis and recurrent blindness (Sharman et al., 1999; Sobolev and Stranadko, 1997; Stranadko et al., 1996; Sokolov et al., 1994).

Despite the clinical success achieved using Photofrin®, this first generation photosensitizer has several important drawbacks. It is a complex chemical mixture produced by the reaction of hematoporphyrin with 5% sulfuric acid in acetic acid followed by treatment with aqueous base and neutralization (Bonnett, 1995). The resulting dimers and oligomers, linked primarily with ester and ether bonds, may vary with different preparations and storage times and make structure-activity relationships impossible to determine (Brown and Truscott, 1993). It absorbs very weakly at the therapeutic wavelength of 630 nm, where tissue penetration of light is minimal, limiting treatment to tumor depths of no more than 5 mm (Wöhrle et al., 1998). While suitable for more superficial lesions presently being treated, absorption at longer wavelengths is necessary to treat more deep-seated or larger tumors. In addition, hematoporphyrin derivatives have proven to be ineffective for such cancers as pigmented melanoma due to overlapping absorption spectra of the photosensitizer and melanin in the malignant tissue

(Peeva et al., 1999). Most importantly, hematoporphyrin derivatives exhibit an extended retention in cutaneous tissue for up to 10 weeks post-injection (Phillips, 1997). This results in a prolonged skin photosensitivity, an obvious disadvantage especially for patients with late stage malignancies. Nonetheless, the prolonged skin sensitivity induced by PDT with Photofrin® is only a mild inconvenience as compared to the severe adverse effects of standard chemotherapeutic regimens. While these disadvantages have not prevented Photofrin® from becoming a useful drug against cancer and other conditions, the search for new second generation photosensitizers with improved physical, chemical and spectral properties remains an important goal (Sharman et al., 1999; Ali and van Lier, 1999).

Ideal photosensitizers for PDT must meet certain criteria, (Bonnett, 1999; Bonnett, 1995; Wöhrle et al., 1998; van Lier, 1988; MacRoberts et al., 1989) namely:

- It should be chemically pure and maintain a constant composition throughout treatment, undergoing minimal photobleaching.
- It should have minimal dark toxicity.
- The photosensitizer should be preferentially retained by the target tissue, whether malignant tumour cells or viral components, so as to induce only marginal toxicity to surrounding healthy biological matter. In addition, the excess dye should be rapidly excreted from the body exhibiting low systemic toxicity.
- The dye should have high photochemical reactivity with a high quantum yield of long-lived triplet-states energetic enough to produce singlet oxygen.
- The sensitizer should have a large absorption coefficient at a long wavelength (600-800 nm) where there is optimal tissue penetration by light with a low degree of

attenuation by hemoglobin. Furthermore, cheaper diode lasers can be used in this range, thus increasing the potential utility of PDT in a clinical setting.

While no photosensitizer can be expected to fulfill all of these parameters, numerous second generation photosensitizers have been investigated that can overcome the shortcomings of hematoporphyrin derivatives and take advantage of their more highly suited properties in order to treat a number of conditions. For instance, the use of 5-aminolaevulinic acid (ALA)-induced endogenous photosensitizers has gained clinical acceptance for the treatment of actinic keratoses of the face and scalp. In the meanwhile verteporfin (benzoporphyrin derivative monoacid ring A) has received market approval in several countries including Switzerland, the United States and Canada, under the trade name Visudyne® as a therapy for wet age-related macular degeneration (AMD) a leading cause of blindness in people over the age of 50. Overall, the photosensitizer used to treat a given condition will greatly depend on the characteristics of the compound and the condition to be treated, with a wide range of different photosensitizers being used in clinic, each for its own particular use. Appendix II outlines the applications of several photosensitizers in pre-clinical and clinical trials.

1.4 Second generation photosensitizers: Phthalocyanines

Among the more promising second generation photosensitizers are phthalocyanines. The term phthalocyanine finds its origin in the Greek word "naptha" which means rock oil and "cyanine" which means dark blue. It was first used to describe this class of macrocyclic compounds by Sir Reginald Linstead in 1933 during his pioneering work on the subject (Linstead, 1934). In addition to the immediate applications as dyes and colorants, it was realized that such compounds would be of great

academic interest. As such, starting in 1929, Linstead and his group began their work on phthalocyanines which lead to the determination of their structure in the early 1930's (Linstead and Lowe, 1934; Dent et al., 1934; Linstead and Robertson, 1936). The synthesis of Pcs and their relationship to porphyrins, along with further examination into the intricate structure of Pcs, their planar nature, their complexes with metal ions and their stability were subsequently studied (Byrne et al., 1934; Linstead and Lowe, 1934; Dent and Linstead, 1934; Dent, 1938; Barrett et al., 1936; Barrett et al., 1938). The structure of phthalocyanines was later confirmed by Roberston via x-ray crystallography in a series of classic papers (Robertson, 1935; Robertson, 1936; Robertson and Woodard, 1937; Roberston and Woodard, 1940). In the seventy years to follow this initial work, a plethora of information emerged concerning diverse synthetic routes, Pc photochemical and photophysical properties and potential applications.

Of the utmost importance is their potential role in photodynamic therapy. These azaporphyrin derivatives have stronger absorbances at longer wavelengths than do porphyrins. Pcs have favorable photophysical and chemical properties. In addition, these properties can be altered through the addition of substituents to the periphery of the macrocycle or axial ligands to the chelated central metal ion. This makes them interesting photosensitizing agents.

Phthalocyanine derivatives have attractive photophysical and photochemical properties as compared to hematoporphyrin derivatives. Monomeric Pcs have a characteristic absorption spectra with a strong Soret absorption peak at approximately 350 nm, a weak maximum around 600 nm and a narrow, very strong, absoption peak in the far red region of the visible spectra (Pc $\lambda_{max} \approx 680$ nm; HpD $\lambda_{max} \approx 630$ nm) where

tissue penetration by visible light is superior. In addition to the red-shift of phthalocyanine Q band absoption maxima, Pcs have an improved capacity to absorb light, by two orders of magnitude over that of the highest Q band absorption of HpDs (Pc molar extinction coefficient (ε) in the 10^5 $M^{-1}cm^{-1}$ range; HpD ε ~10^3 $M^{-1}cm^{-1}$) (van Lier et al., 1988; van Lier and Spikes, 1989). These qualities therefore lead to enhanced photophysical and photochemical properties.

The nature of the central metal ion influences the Pc photophysical properties (triplet quantum yield and lifetime). Complexation of Pcs with open shell or paramagnetic metal ions such as Cu^{2+}, Co^{2+}, Fe^{2+}, Ni^{2+}, VO^{2+}, Cr^{3+} and Pd^{2+} give dyes with shortened triplet lifetimes (nanosecond range) due to increased intersystem crossing back to the ground state, which renders the dye photoinactive (Chan et al., 1987). Pcs containing closed d shell or dimagnetic metal ions, such as Zn^{2+}, Al^{3+} and Ga^{3+}, are dyes producing high triplet yields ($\phi_T > 0.4$) with long lifetimes ($\tau_T > 200$ μs) (Darwent, 1982). These triplet M-Pcs vary in energy from 110-126 kJ/mol which is ample energy to generate singlet oxygen (94.5 kJ/mol) with high quantum yields (ϕ) of approximately 0.3-0.5 (Wagner et al., 1987). Singlet oxygen yields are affected by ring substituents and axial ligands. Phthalocyanines tend to aggregate or dimerize which in turn determines the $MPcS_n$ activity (Wagner et al., 1987). Aggregation is easily detected spectroscopically as absorption occurs at shorter wavelengths in the Soret region and there is a 30-50 nm blue-shift of the Q band absorption peak which appears more broad and less intense. Disaggregation to form monomeric dyes can be accomplished by adding detergents, serum or plasma proteins or organic solvents (van Lier and Spikes, 1989; Ben Hur et al., 1987).

1.4.1 Phthalocyanine induced apoptosis or necrosis

Phthalocyanines are very potent photosensitizers for use in PDT. Since first reported, several differently substituted Pc molecules have been synthesized and their PDT potential evaluated. Preliminary PDT results were promising using Pc derivatives, thus prompting more in depth studies regarding mode of cell death.

Apoptosis is a notable mode of cell death in response to PDT using phthalocyanines (Oleinick, 1998). A promising phthalocyanine receiving a great deal of attention is the silicon Pc, denoted as Pc4, bearing a long chain amino axial ligand ($HOSiPcOSi(CH_3)_2(CH_2)_3N(CH_3)_2$). This silicon phthalocyanine has shown promising results both *in vitro* and *in vivo*. Axial ligated Pcs have an important advantage over Pcs substituted on the periphery. Not only does the axial ligand impart greater solubility and prevent aggregation, these compounds do not have isomers, thus simplifying the preparation of pure samples.

Pc4 has been shown to initiate an apoptotic response in several cell lines including L5178Y-R cells. DNA fragmentation, a hallmark of apoptosis, was observed (He et al., 1997). This same research team demonstrated the importance of cell membrane damage with respect to apoptosis induction. Photodamaging the cell membrane initiates a cascade of events such as phospholipase C activation, release of secondary messengers and an increase in intracellular calcium concentration, all leading to cell suicide (Agarwal et al., 1993). Furthermore, an increase in intracellular calcium concentration also leads to the formation of nitric oxide (NO), an important bioactive signaling molecule. It has been demonstrated that NO is involved in PDT-mediated apoptosis (Gupta et al., 1998). In addition to NO, other well documented apoptotic

pathways are initiated by Pc4-PDT. Cytochrome c is released into the cytosol and subsequent activation of proteases, (Varnes et al., 1999) now known as caspases, resulting in the cleavage of various proteins including poly(ADP-ribose)polymerase have been documented (He et al., 1998). Cell cycle arrest in the G0/G1 phase of the cell cycle as a result of p21 induction has been observed following Pc4 therapy (Agarwal et al.,1993). In addition, the participation of retinoblastoma protein has been studied following phototherapy (Ahmad et al., 1998). Several other apoptotic pathways and proteins involved in PDT mediated apoptosis are under investigation.

Furthermore, enhanced apoptotic responses to photodynamic therapy with AlPc was observed after bcl-2 transfection (Choi Kim et al., 1999). Bcl-2 is a known inhibitor of apoptosis via antagonizing the release of mitochrondrial cytochrome c. In this case, using immortalized MCF10A cells, overexpression of bcl-2 and bax was revealed and PDT caused selective destruction of bcl-2, leaving bax unaffected. As such, the greater apoptotic response towards PDT in this case is probably attributed to the higher bax:bcl-2 ratio after photodamage. On the other hand, CHO-K1 cells transfected with Bcl-2 exhibited a partial resistance to PDT-induced cell death, either via apoptosis or non-apoptotic mechanisms (He et al., 1996).

Subsequently, it was demonstrated that the mode of cell death is not only dependant on cell type (i.e. fibroblasts do not die via organized DNA fragmentation (He et al., 1997)) but also on the photosensitizer, its intracellular localization and the drug and energy dose administered. In addition, it has recently been shown that the mode of cell death also varies with cell density due to the bystander effect (Dahle et al., 1999). Using AlPc and lower PDT doses resulted in the induction of apoptosis as opposed to necrosis.

Organelles such as the mitochondria and lysosymes were mainly affected. At higher PDT doses, cells underwent severe membrane damage resulting in necrosis (Luo and Kessel, 1997). Interestingly, Dellinger reported a mixed response when using Photofrin® and CV-1 cells (Dellinger, 1996). At higher irradiation doses, the cells lysed instead of exhibiting fragmentation associated with apoptosis. However, morphological changes typical of apoptosis were observed initially, such as plasma membrane blebbing, condensation of the cytoplasm and nuclear fragmentation. These cells appear to enter an apoptosis-like death, yet this pathway is stopped by plasma membrane lysis and ultimately, the cells undergo necrosis. *In vivo* studies using the murine MS-2 fibrosarcoma tumor model demonstrated random necrosis of tumor cells post ZnPc-PDT. Interestingly, apoptotic pathways were also detected, suggesting different localization of photosensitizers within the cell upon illumination (Jori and Fabris, 1998).

Photodynamic therapy using phthalocyanines is known to induce a number of responses that ultimately lead to apoptosis. For instance, PDT using Pc4 induces an oxidative stress associated with increased ceramide generation (Separovic et al., 1997), which has been associated with apoptosis in several malignant and non-malignant cell lines. The increased production of ceramide is due to the stress-induced activation of sphingolyelinase (SMase). It has been shown that normal human lymphoblasts accumulate ceramide and undergo apoptosis following Pc4-PDT. In contrast, Niemann-Pick disease lymphoblasts, which are deficient in acid sphingomyelinase, fail to respond to Pc4-PDT via ceramide accumulation and apoptosis (Separovic et al., 1999). However, addition of exogenous bacterial Smase during Pc4-PDT induced a significant apoptotic response. This lead to the hypothesis that SMase may be an important proapoptotic

factor determining responsiveness of cells to Pc4-PDT. Previous work showed that Pc4-PDT was able to induce apoptosis in numerous cell lines. Three cell lines were studied *in vitro* revealing the accumulation of ceramide post PDT and induction of apoptosis. Interestingly, there were increased levels of ceramide in RIF-1 cells post PDT with no evidence of apoptosis. Ceramide clearly is associated with PDT-mediated cell death either by inducing apoptosis or necrosis (Separovic et al., 1998).

1.4.2 Phthalocyanine delivery systems

Targeting of photosensitizers is imperative, as singlet oxygen is extremely reactive thus limiting PDT action to the site of singlet oxygen generation. As previously stated, its lifetime in biological systems has been estimated to be 200 ns with a diffusion range of 45 nm (Ochsner, 1997). Mammalian cells are 10^4 to 10^5 nm in diameter thus the importance of PS distribution within the target tissue is evident. Hydrophobic sensitizers have been shown to be biologically beneficial as compared to hydrophilic compounds. The former exhibits greater photocytotoxicity and tumor eradication, most probably because these hydrophobic dyes localize in more photosensitive cellular compartments. However in aqueous solutions, photosensitizers, either non-substituted or substituted with hydrophilic groups, tend to aggregate and dimerize which affects their cell penetrating properties and results in a loss of photochemical activity. Increased photodynamic action has been attributed to increased monomerization of the photosensitizer.

Lipophilic photosensitizers require biologically compatible delivery systems. Nanoparticles have received attention as potential delivery vehicles for drug targeting. A hexadecafluoro zinc phthalocyanine was formulated in polyethylene-glycol-coated poly(lactic acid) nanoparticles and evaluated for PDT efficiency. Using the EMT-6

tumor model, improved tumor response was observed using the nanoparticle formulation as compared to the same dye solubilized in Cremophor EL (Allémann et al., 1996). Nanoparticle formulation allows for increased serum levels of the dye as compared to Cremophor EL (CRM) formulation. Increased blood levels and enhanced tumor uptake lead to higher tumor-to-organ concentration ratios enhancing the overall dye efficacy (Allémann et al., 1995). Likewise pH-responsive, polymeric micelles consisting of random co-polymers of *N*-isopropylacrylamide, methacrylic acid and octadecyl acrylate have been loaded with water-insoluble AlPc and shown to exhibit higher phototoxicity against EMT-6 cells *in vitro* than the control CRM preparation (Taillerfer et al., 2000).

In addition to emulsifiers such as Cremophor EL, Solutol HS or lipid-based vehicles such as liposomes, a substantial amount of research has focused on proteinic carriers for improved targeting of malignant cells. Serum lipoproteins can incorporate hydrophobic sensitizers into their lipid portion. Frequently, neoplastic cells have increased LDL receptors on the cell surface as increased proliferation requires cholesterol for membrane synthesis (Vitols, 1991). Subsequently, LDL are known to deliver photosensitizers to neoplastic cells through a receptor internalization mechanism (Hamblin and Newman, 1994; Mazière et al., 1991; Allison et al., 1994). Jori and associates have done extensive studies using ZnPc incorporated into liposomes of varying composition. As will be discussed in greater detail later, Jori et al. have investigated the role of serum lipoproteins and found them to be effective delivery vehicles for phthalocyanines (Polo et al., 1995; Reddi, 1997; Reddi et al., 1990; Valduga et al., 1999).

Recently, a series of publications has reported the use of a modified aluminum tetrasulfophthalocyanine covalently coupled to various proteins via one or two caproic

acid spacer chains. Brasseur et. al. targeted the scavenger receptor of macrophages using a maleylated bovine serum albumin covalently labeled with $AlPcS_4$. Relative photocytotoxicities were reported using a receptor positive and a receptor negative cell line where their lethal effects correlated with receptor affinity for the BSA-Pc conjugate (Brasseur et al., 1999).

Using the same phthalocyanine derivative, it was found that covalently labeling a monoclonal antibody for the CD3+ antigen in a similar manner did not hinder receptor recognition. There was increased uptake of the antibody-Pc conjugate in a receptor positive cell line as compared to the free phthalocyanine and antibody-Pc uptake was less in a cell line void of receptors (Ménard, 1998). However, the Pc-antibody conjugates were photoinactive, most likely due to inefficient subcellular targeting. Similarly, $AlPcS_4$ was covalently coupled to monoclonal antibodies directed against carcinoembryonic antigen (CEA) (Carcenac et al., 1999). *In vivo* studies using nude mice bearing human colon carcinoma xenografts (T380) demonstrated increased uptake of the antibody-Pc conjugate as compared to the free Pc. *In vitro* results were encouraging using this antibody complex.

1.5 Research objectives

Over the past 20 years, several photosensitizers have been synthesized and tested both *in vitro* and *in vivo* with varying results. Initially, this approach to PDT was sufficient. However, more elaborate research is now underway to improve efficiency by targeting the photosensitizer (PS) to various tissue types. A number of second generation photosensitizers such as phthalocyanines are effective drugs for PDT. However, to improve tumor uptake and preferential tumor-to-normal tissue ratios, third generation photosensitizers are being designed where the chromophore is tagged with a targeting system in order to improve these characteristics.

The current research is sub-divided into four categories as represented by four research papers that have been published or submitted for publication as part of the present study. Chapter 2 presents results of a study employing a series of AlPc derivatives substituted with aliphatic chains of varying lengths on the Pc macrocycle imparting different lipophilicity. Amphiphilicity plays a major role in determining the usefulness of a Pc for PDT. The first study investigates the PDT potential of a series of amphiphilic AlPc derivatives as a function of lipophilicity. This study tests the hypothesis that amphiphilic phthalocyanines have improved PDT potential.

Subsequently, the role of low-density lipoproteins (LDL) as vehicles for AlPcS delivery to target tumor cells was evaluated and reported in chapter 3. Parallel studies using both non-covalently labeled and covalently labeled LDL to target human adenocarcinoma lung cancer cells (A549) were carried out. The amphiphilic $AlPcS_4$ molecule bearing a twelve-carbon alkyl side chain on the Pc macrocycle was noncovalently inserted in the LDL phospholipid layers. $AlPcS_4$ was covalently coupled to

the apolipoprotein moiety via two sulfonamide five-carbon spacer chains. The two fold question addressed was whether or not LDL molecules are suitable vehicles for Pc delivery to the target tissue and whether Pc attachment to the protein or the lipid portion of the LDL affects PDT.

Using the same principle, adenoviral proteins were employed to target lung cancer cells rich in the appropriate class of integrin receptors. Adenoviruses have been receiving a great deal of attention as gene therapy vectors. These viral particles gain entrance into the cells via receptor mediated endocytosis. Two receptors are required, the first for attachment and the other mediating internalization. Internalization of the virus particle is via integrin receptors able to bind with high affinity to the RGD binding motif found in the penton base protein of adenovirus. Chapter 4 outlines studies using the adenovirus capsid proteins covalently labeled with $AlPcS_4$ derivatives. Is Pc delivery to cells improved and is PDT more efficient as a result of this?

Tumor targeting using protein vehicles may have serious limitations invoking adverse immune responses. The search for small peptidic vectors was the rational behind the fourth objective of this thesis as described in chapter 5. The RGD peptide sequence is currently being investigated as a targeting vehicle for conventional chemotherapeutics. The present study evaluated the effects of RGD on cell survival following $AlPcS_{2adj}$ photodynamic treatment of both a receptor negative and a receptor positive cell line. Does RGD enhance Pc-PDT?

Chapter 2.

Photodynamic properties of amphiphilic derivatives of aluminum tetrasulfophthalocyanine

Cynthia M. Allen, Réjean Langlois, Wesley M. Sharman, Carole La Madeleine and Johan E. van Lier (2002) *Photochem. Photobiol.* **76**, 208-216.

Chapter 3.

Low Density Lipoprotein-Bound Aluminum Sulfophthalocyanine: Targeting Tumor Cells for Photodynamic Therapy

Pascale Urizzi, Cynthia M. Allen, Réjean Langlois, René Ouellet, Carole La Madeleine and Johan E. van Lier (2001) *J. Porphyrins and Phthalocyanines* **5**, 154-160.

Chapter 4.

Symposium-in-Print

Photodynamic therapy: Tumor targeting with adenoviral proteins

Cynthia M. Allen, Wesley M. Sharman, Carole La Madeleine, Joseph M. Weber, Réjean Langlois, René Ouellet and Johan E. van Lier (1999) *Photochem. Photobiol.* **70**, 512-523.

Chapter 5.

Attenuation of photodynamically induced apoptosis by an RGD containing peptide

Cynthia M. Allen, Wesley M. Sharman, Carole La Madeleine, Johan E. van Lier and Joseph M. Weber (2002) *Photochem. Photobiol. Sci.* **1**, 246-254.

Chapter 6.

Discussion

6. Discussion

Second generation photosensitizers have several advantages over hematoporphyrin derivatives. However even the most potent chemotherapeutic agents are of no use if they don't target the desired tissue and can have deleterious effects. This alone outlines the importance of drug targeting.

6.1 Amphiphilic phthalocyanines

Substituents on the phthalocyanine framework have included aliphatic chains and higher order aromatics to improve both the solubility and potential usefulness of the Pc. The current study uses $AlPcS_4$ substituted with aliphatic chains of increasing length. In general, amphiphilic molecules have been found to be more photodynamically active. The hydrophobic chain portion can slip into the cell membrane and anchor the Pc while their charged sulfonate groups interact with the aqueous layer outside the cell. Following 48 hours incubation, the highest cellular concentration was observed with the more lipophilic $AlPcS_4$(C16) derivative followed by the C12 < C8 < C4. The more hydrophilic compounds accumulated to a less extent. The $AlPcS_{2adj}$, having a similar retention time on the HPLC column as the $AlPcS_4$(C12), also had comparable A549 cell uptake properties. It is important to stipulate cell type as different cell types may exhibit different membrane permeation of the different Pc molecules. In addition, decreasing aggregation of the phthalocyanine enhances cell uptake of the sensitizer. In the present study the $AlPcS_4$(C16) was initially solubilized in methanol then further diluted in PBS. The methanol was evaporated off leaving only trace amounts. Studies where the $AlPcS_4$(C16) derivative was dissolved directly in PBS resulted in different uptake by the

cells of the photosensitizer and the phototoxicity of the sensitizer was altered. This is most likely due to increased sensitizer aggregation.

To circumvent such problems as aggregation but to retain the amphiphilic nature of the sensitizer, a series of silicon phthalocyanines with charge axial ligands was synthesized and tested on the EMT-6 cell line (Murphy et al., 2001). Axial ligated Pcs have an important advantage over Pcs substituted on the periphery. Not only does the axial ligand impart greater solubility and prevent aggregation these compounds do not have isomers, thus simplifying the preparation of pure samples. The SiPc in this study, with the longest axial ligand thus the more amphiphilic, was most phototoxic. This is comparable to the present study where the $AlPcS_4(C16)$ molecule was most photoactive. This increased length of the axial substituent presumably helps the dye to better partition into the membrane. A promising amphiphilic phthalocyanine receiving a great deal of attention is the silicon Pc, denoted as Pc4, bearing a long chain amino axial ligand ($HOSiPcOSi(CH_3)_2(CH_2)_3N(CH_3)_2$). Clinical trials are scheduled to begin in 2001 (personal communication).

6.2 Protein carriers

Site-specific drug delivery is an integrated part of the intellectual and experimental design of a therapeutic system. Enhanced delivery systems can access previously inaccessible cellular compartments thus reducing the amount of drug administered and protecting the body from unwanted accumulation and toxicity. The dye must be exclusively delivered to the pharmacological site of action at an appropriate dose to effectively combat the disease and improve the therapeutic index. As the pathophysiology of various diseases becomes known, researchers can exploit cellular

systems to increase dye uptake. Receptor-mediated endocytosis allows for the uptake and intracellular processing of macromolecules that bind to the cell surface receptors. Endocytosis of the plasma membrane is a continuous activity in many cell types occurring at a constant rate regardless of external stimuli. In this way, cell surface receptors are regularly re-distributed to the plasma membrane. Receptor internalization can also be stimulated by ligand binding. It has been estimated that 80% of the epidermal growth factor (EGF) receptors internalize within a half time of 2.5 minutes upon binding saturation (Hopkins, 1986). In view of this, drug trafficking across the cell plasma membrane is feasible. Additionally, protein carriers specifically targeting a cellular population will decrease liver entrapment of the photosensitizers as the drug package is strictly addressed. Several protein/receptor systems have been explored for the purpose of drug delivery.

We report that the presence of 4 μg/mL of LDL slightly enhances the phototoxicity of the $AlPcS_4$ derivatives substituted with long chains. Naturally, the next phase in this study was to incorporate these lipophilic sensitizers with LDL prior to administration. This was accomplished either via covalent or non-covalent coupling of the Pc to the LDL. Extensive studies have investigated serum proteins as drug carriers and merit acknowledging.

6.3 Serum proteins

Serum proteins are predominantly responsible for the transport of photosensitizers throughout the body. Serum albumin generally transports hydrophilic PS whereas more hydrophobic PS localize preferentially in lipoproteins, leading to enhanced intracellular accumulation of the dye via receptor mediated endocytosis (Table 6.1) (Rosenthal, 1991;

Reddi, 1997; Hamblin and Newman, 1994a). To further benefit from this, coupling of photosensitizers with albumin and low-density lipoproteins (LDL) prior to administration has been investigated as a means to deliver PS with higher target specificity.

6.3.1 Albumin

Initial studies involved the non-covalent binding of PS to bovine serum albumin (BSA) prior to intravenous administration (Larrocque et al., 1996). Using two *in vivo* tumor models, murine mammary carcinoma and human colon carcinoma, tumor regression was observed at ZnPc doses of 0.5 and 2.0 μmol per kg respectively.

Alternatively, covalent conjugates were prepared using BSA and various photosensitizers. These biomolecules can enter the cell either via passive diffusion or via receptor mediated endocytosis. Tumor-associated macrophages accumulate higher levels of photosensitizer as compared to neighboring tumor cells (a nine fold increase in the case of porphyrins) (Hamblin and Newman, 1994b). It has been estimated that in several cancers over 50% of the tumor mass is of the macrophage lineage. Macrophages express high numbers of the scavenger receptor which is able to bind a wide range of ligands, shuttling them to endosomes and lysosomal compartments. This receptor readily binds oxidized LDL and maleylated bovine serum albumin but not the corresponding native proteins (Krieger et al., 1993). Thus by covalently attaching photosensitizers to the BSA molecule, specific targeting of this receptor ensues.

Brasseur et al. reported that maleylated-BSA was covalently coupled to $AlPcS_4$ via one or two sulfonamide hexanoic amide spacer chains. The photosensitizers used in the preparation of these bioconjugates is the same as that used in the covalent labeling of the adenoviral proteins (chapter 4) and the LDL molecules (chapter 3). The Pc-conjugate

was readily taken up by the scavenger receptors on J774 cells. Mal-BSA-Pc was more photocytotoxic against this receptor-bearing cell line compared to a negative control (Brasseur et al., 1999). Similarly, mal-BSA coupled to chlorin e6 exhibited increased PS accumulation and phototoxicity when using J774 cells as compared to non-target OVCAR-5 cells (Hamblin et al., 2000a; 2000b). Dye uptake was decreased after incubating the mal-BSA-Ce6 with the cells at 4°C, indicating an endocytotic route of entry.

6.3.2 Lipoproteins

The current study evaluates low density lipoproteins (LDL) as potential dye carriers. LDL are particles that are naturally produced by the liver. Their primary role is to transport cholesterol and other lipids to various cells throughout the body. They possess a receptor-binding motif, apolipoprotein B-100, which binds with high affinity to a LDL cell surface receptor and is subsequently internalized. Cancer cells naturally express greater numbers of these receptors, making LDL particles attractive vehicles for drug targeting (Gueddari et al., 1993).

Early *in vivo* studies showed that very hydrophobic photosensitizers could only be administered following inclusion in lipid material (Reddi et al., 1990). Therefore ZnPc was enclosed in various liposomes. Several studies have investigated the interactions of LDL and liposomes containing ZnPc to determine whether the ZnPc becomes incorporated in the LDL (Valduga et al., 1999; Versluis et al., 1994; Rensen et al., 1994). Following *in vitro* incubation of the LDL and liposomes, the LDL particles acquired a net negative charge as seen using electrophoretic mobilities. This is indicative of ZnPc loading into the LDL. Consequently, intravenous injection of liposomal Pc showed that

LDL particles were indeed involved in Pc transport. Therefore, studies in which the ZnPc was non-covalently complexed with LDL *prior* to injection showed a two-fold greater tumor uptake of the Pc than when the Pc was enclosed in DPPC liposomes (Reddi et al., 1990). Accordingly, the use of the LDL receptor pathway as a tool for enhancing the selectivity of PS delivery to tumor cells has been extensively studied (Mazière et al., 1991; Jori et al., 1993).

AlPc was non-covalently incorporated into oxidized LDL and the photodynamic efficiency evaluated. The oxidized LDL-Pc complex was taken up by the scavenger receptor after incubation with macrophages. Incubation of this Pc-LDL complex in serum revealed that it was quite stable, showing very little re-distribution amongst the other serum components (de Vries et al., 1999). In addition, LDL were non-covalently labeled with hematoporphyrin. Selectivity of tumor targeting was prominent. Electron microscopy demonstrated that the Hp-LDL conjugate induced direct tumor cell kill as opposed to the indirect effect seen when free Hp is administered. This suggested that targeting was through the LDL receptor pathway as the Hp-LDL seemed to be taken up by the cells via receptor-mediated endocytosis (Zhou et al., 1988).

Chapter 3 outlines the study whereby $AlPcS_4$ with a twelve carbon alkyl chain (C_{12}) was non-covalently inserted into the phospholipid moiety of the LDL (Figure 3.1). *In vitro* PDT studies on adenocarcinoma lung cancer cells (A549 cells), which have increased LDL receptor expression, using the $AlPcS_4C_{12}$ conjugate were very effective (Urizzi et al., 2001). The $AlPcS_4C_{12}$-LDL conjugate was twice as phototoxic as compared to the $AlPcS_4C_{12}$, whereas, under similar experimental conditions, the parent molecule, $AlPcS_4$, was inactive. The $AlPcS_4C_{12}$-LDL bioconjugate was more

photoactive against the EMT-6 cell line. At doses as low as 0.2 μmol kg^{-1}, tumor regression was observed using the bioconjugate against the murine EMT-6 model. However as shown in chapter 2, the $AlPcS_4$ derivatives substituted with long side chains exhibit similar tumor response and did not require coupling of the Pc with LDL prior to administration.

While non-covalent labeling of LDL particles showed promise, attempts to make covalent conjugates have been disappointing. LDL were covalently coupled with $AlPcS_4$ bearing two sulfonamide five carbon chains (A_2) (Figure 3.1). Covalent coupling of the LDL protein moiety via the carboxylic acid groups of the monocaproic acid substituents reduced receptor recognition, thus decreasing cell/LDL-Pc interactions. Molar Pc:LDL ratios of approximately 70:1 were maintained as this represented 90% labeling yield. Perhaps decreasing this ratio would enhance cell uptake of the bioconjugate leading to increased phototoxicity. This Pc conjugate was photo-inactive at the highest drug and light doses studied. An alternative explanation could be altered trafficking upon internalization, without redistribution of the Pc to more photo-susceptible sites within the cell. Likewise, Hamblin and Newman conjugated LDL with hematoporphyrin via an amide bond which is similar to the present study (Hamblin and Newman, 1994c). Confocal microscopy showed that Hp-LDL localized in lysosomal compartments and that the LDL receptor was not solely responsible for uptake of this conjugate. Phagocytosis played a key role as well.

Alternatively, other photosensitizers have been covalently attached to LDL via carbodiimide activation such as chlorin e6 (Schmidt-Erfurth et al., 1997). LDL receptors on retinoblastoma cells were targeted. There was a 5-fold increase in chlorin e6 uptake

when using the LDL-Ce6 conjugate as compared to free Ce6. Similarly, the LDL-Ce6 complex was very phototoxic. These results suggest that LDL could be used as dye carriers for intraocular tumors such as retinoblastomas thus avoiding invasive treatments.

BPD non-covalently associated with LDL was likewise used to treat ocular conditions. It was observed that BPD-LDL accumulation was insignificant in LDL receptor negative fibroblasts or when the LDL was chemically modified. Furthermore, *in vivo* studies in M1 tumor bearing DBA/2J mice showed a pronounced enhancement of BPD-native LDL tumor accumulation over that of acetylated LDL associated BPD (Allison et al., 1994). These results indicate that the LDL receptor is responsible for the uptake of the BPD-LDL. Subsequently, BPD-LDL photodynamic therapy was tested on an experimental model of choroidal melanoma (Schmidt-Erfurth et al., 1994), experimental choroidal neovasculature (Miller et al., 1995) and Greene melanoma (Schmidt-Erfurth et al., 1996). Results were favorable in all three models indicating LDL usefulness as a sensitizer delivery vehicle.

Table 6.1 Summary of photosensitizer serum-based vehicles and bioconjugates

Vehicle	Photosensitizer	Target	Reference
Albumin (BSA)	Hematoporphyrin	Macrophages	Hamblin and Newman 1994
Albumin (BSA)	ZnPc	Murine mammary and human colon carcinoma	Larroque et al. 1996
Albumin (BSA), Fibrinogen, Gelatin	Chlorin e6	Tissue solder	Khadem et al., 1999
Maleylated BSA	Chlorin e6	Scavenger receptor Intimal hyperplasia	Nagae et al. 1998
Maleylated BSA	$AlPcS_4A_1$ and A_2	Scavenger receptor	Brasseur et al. 1999
BSA and Maleylated BSA	Chlorin e6	Scavenger receptor	Hamblin et al. 2000
LDL	ZnPc	MS-2 fibrosarcoma	Reddi et al 1990
LDL	$TPPS_n$	LDL receptor on human hepatocyte tumor	de Smidt et al 1993
LDL (human)	BPD-MA	Choroidal melanomas, choroidal neovasculature	Schmidt-Erfurth et al 1994 Miller et al., 1995
LDL, HDL	Hematoporphyrin	LDL receptor on fibroblast Scavenger receptor	Hamblin and Newman, 1994 Hamblin and Newman, 1994
LDL	BPD-MA	LDL receptor on rhabdomyosarcoma	Allison et al 1994
LDL (human)	BPD-MA	Greene melanoma	Schmidt-Erfurth et al 1996
LDL (human)	Chlorin e6	Retinoblastoma	Schmidt-Erfurth et al 1997
LDL (oxidized)	AlPc	Scavenger receptor	Devries et al 1999
LDL	$AlPcS_4A_2$ and $AlPcS_4(C_{12})$	LDL receptor of lung adenocarcinoma	Urizzi et al 2000
Transferrin	Hematoporphyrin	Transferrin receptor	Hamblin et al. 1994

6.4 Antibody conjugates

A class of protein vehicles is the antibody vehicles. Photodynamic therapy using PS-Ab conjugates, termed photoimmunotherapy (PIT), has been developed over the past 15 years (Hasan et al., 1997; Klyashachitsky et al., 1994). PIT has evolved in parallel with the use of monoclonal antibodies as pharmaceuticals. PIT is an ever-expanding field of study as mAb generation techniques improve thus generating different antibodies to be coupled with various photosensitizers. Targeting of photosensitizers using antibodies and/or fragments has been extensively investigated. Table 6.2 is a summary of various studies.

6.4.1 Phthalocyanines

Phthalocyanines have likewise been targeted to various cell lines via antibody carriers. $AlPcS_n$ was encapsulated in liposomes that were then linked to antibodies for targeting purposes. It was clear from these early studies that the phototoxicity was directed by the mAb because free Pc or liposomal Pc were not phototoxic against the antigen-bearing cell lines under the same conditions (Morgan et al., 1989). Subsequently, this liposomal $AlPcS_n$ formulation was used to target B-cells using an anti-B-cell Ab as well as T-lymphocytes using anti-CD3 antibody. This could be applicable for *ex vivo* bone marrow purging (Morgan et al., 1992). A similar method has also been used to target human bladder carcinoma (Morgan et al., 1994). An $AlPcS_4A_1$ (A_1 being a 5 carbon spacer chain) has been used to label anti-carcinoembryonic antigen (CEA) monoclonal antibodies. This is the same Pc derivatives used to label proteins in the current study. The Pc-mAb conjugates had 5-16 moles of Pc per mol of antibody. The immunoreactivity of the bioconjugates was not altered due to the coupling with a

photosensitizer. In nude mice, tumor to normal tissue ratios were similar for the Pc-mAb conjugates as compared to the free antibody. *In vitro*, the bioconjugate was photocytotoxic against antigen positive cells. This, taken together with the *in vivo* tumor seeking capacity of the Pc-mAb, makes it a promising third generation photosensitizer (Carcenac et al., 1999). Conversely, an anti-CD3 antibody was covalently labeled with $AlPcS_4A_1$. Cell uptake of the bioconjugate was not impaired as measured by flow cytometry. However, the bioconjugate was not photoactive (Ménard, 1998). It was postulated that upon internalization of the Pc-mAb, the photosensitizer was trapped in the endosome and following illumination, the singlet oxygen produced was quenched by the Pc-mAb microenvironment.

Table 6.2 Summary of photosensitizer-antibody conjugates

Antibody	Photosensitizer	Target	Reference
Rabbit anti-Hu CAMAL-1 L1210	Hematoporphyrin	Human perpherial blood leukocytes CAMAL antigen Irrelevant MoAb	Mew et al., 1985
Anti-Leu/1	Chlorin e6	T-leukemia cells	Oseroff et al., 1986
Mab 3G2/C6	Chlorin e6	Bladder carcinoma	Hasan et al., 1989
Mab 791T/36	Liposomal AlPcS	Osteosarcoma, colorectal carcinoma	Morgan et al., 1989
Mab 3G9 Mab 3H11	Hematoporphyrin derivative	Gastric cancer	Xu et al., 1989
Mab T48	BPD-MA	Human chorionogonadotropic (HCG) hormone	Jiang et al., 1990
Rabbit IgG anti-E.coli	Iodinated fluorescein	E. coli	Devanathan et al., 1990
Mab OC125	Chlorin e6	Ovarian carcinoma	Goff et al., 1991, 1994, 1996 Hamblin et al., 1996
Mab HMFG-1	Hematoporphyrin	Breast adenocarcinoma	Prosser et al., 1991
Mab E7	Liposomal AlPcS	Urinary bladder carcinoma	Morgan et al., 1994
Mab OC125	Chlorin e6	Human ovarian cancer	Duska et al., 1997
Mab OKT3	$AlPcS_4A_1$	Leukemic T lymphocytes (CD3+)	Menard, 1998
Mab U36	m-THPC	Head and neck squamous cell carcinoma	Vrouenraets et al., 1999
Mab 35A7	$AlPcS_4A_1$	Carcinoembryonic antigen (CEA)	Carcanac et al., 1999
Mab U36 Mab 425	TrisMPyP-ΦCO_2H	Squamous cell carcinoma	Vrouenraets et al., 2000
Murine Mab 17.1A	Chlorin e6	Human colorectal cancer antigen (EpCMA)	Del Governatore et al., 2000(a, b) Hamblin et al., 2000

6.5 Epidermal growth factor

Epidermal growth factor (EGF) is a small protein that binds to a cell surface receptor. EGF is a potent mitogen found throughout the body and is classified as an angiogenesis stimulating factor. As seen with integrin receptor expression, the EGF receptor (EGF-R) is over expressed in a variety of tumor types, in particular ovarian cancers. 30% of ovarian cancers have increased EGF receptor numbers, making EGF a potential drug carrier (Moor et al., 2000). EGF has been coupled to various photosensitizers in the hopes of specifically targeting this receptor. The cytotoxic activities of an AlPc and a CoPc bound to EGF were determined against a human breast carcinoma cell line. The AlPc-EGF was seven times more photoactive as compared to the free AlPc. The CoPc-EGF conjugate was cytotoxic, requiring ascorbic acid for activation as opposed to light. *In vivo* studies using B16 melanoma were subsequently carried out (Lutsenko et al., 1999).

More elaborate conjugates have been prepared using EGF and Sn(IV)chlorin e6 bound together via carriers such as dextran, polyvinyl alcohol and human serum albumin (HSA) (Gijsens and de Witte, 1998; Gijsens et al., 2000). The EGF-HSA-SnCe6 conjugate had the best receptor affinity displaying high phototoxicity against a cell line over-expressing the EGF-R. The effect was receptor related as native EGF could compete for binding sites and decreased photoactivity. The HSA conjugate also produced more intracellular ROS upon irradiation as compared to the dextran conjugate. In a previous study, the EGF-Dex-SnCe6 conjugate bound specifically to the EGF receptor on a squamous cell carcinoma line whereas the EGF-PVA-SnCe6 conjugate

displayed limited binding. It was concluded that the photodynamic activity of these conjugates was dependent on the carrier used.

6.6 Adenoviral Carriers

Adenoviral proteins were studied as protein carriers for $AlPcS_4$ (chapter 4). Adenoviruses have natural tropism for a variety of tissue types. Adenoviruses enter cells via receptor mediated endocytosis involving two separate receptors. The first one, designated as CAR (Coxsacchi and Adenovirus Receptor), is responsible for mediating attachment while the second receptor is responsible for internalization. This second receptor is a member of the integrin class of surface receptors. As previously stated, integrin receptor expression is frequently altered in cancer cells. Studies have shown that human lung cancer cell lines such as A549 (used in the current study) have increased expression of RGD binding integrins on the cell surface (Hirasawa et al., 1994). This would suggest that adeno-vectors could function as selective carriers to deliver photosensitizers specifically to lung cancer cells.

Adenovirus type 2 capsid proteins were covalently labeled using an $AlPcS_4$ derivative via one or two caproic acid spacer chains (Figure 4.2). The specific adenovirus capsid proteins, the hexon, the penton base and the fiber were purified and conjugated with the Pc. The purification procedures were long and tedious resulting in only minimal amounts of purified proteins. Therefore, a mixture of adenovirus type 2 soluble proteins was also covalently coupled with $AlPcS_4A_2$. The bioconjugates were found to be only slightly photoactive *in vitro* when using the receptor positive cell line, A549 cells. *In vivo* studies were more promising. The Ad2-soluble protein mixture labeled with the $AlPcS_4A_2$ derivative, at doses of 0.5 $\mu mol\ kg^{-1}$ and 400 $J\ cm^{-2}$, resulted

in complete tumor regression using the EMT-6 model. This was a 20 fold decrease in Pc dose as compared to the parental $AlPcS_4$. Within the adenoviral protein mixture, the appropriate combination of viral proteins may be present invoking endosomal degradation to release the Pc. Endosomal entrapment of the photosensitizer has been proposed as an explanation for the decreased photocytotoxicity induced by the Pc conjugated with the purified penton base. This would prevent targeting of the PS to susceptible intracellular sites.

Increased cell uptake of the bioconjugate over that of the free Pc was seen, as would be expected due to the presence of integrin surface receptors that can readily bind the RGD motif of the penton base. However, there was only marginal cell kill after irradiation *in vitro*. Several factors are required to release the contents of the endosome upon internalization, in particular the adenoviral protease (Cotton and Weber, 1995). Therefore one could foresee using an attenuated adenovirus covalently labeled with a phthalocyanine as a delivery vehicle. The virus could be modified in such a way as to express one or more integrin binding ligands (RGD sequences) at the knob of the fiber protein. Upon binding via the RGD/integrin interaction, the virus-Pc would be internalized. The subsequent release from the endosome would be facilitated due to the use of an intact viral particle.

Sophisticated experiments were conducted using chlorin e6 as a photosensitizer, insulin as an internalizable ligand and the SV40 large T antigen as a nuclear localizing signal. These were all bound to BSA, a protein carrier. This conjugate was co-administered with an attenuated adenovirus (Akhlynina et al., 1999). Insulin/receptor complexes are internalized into endosomes and this is a limiting factor in the nuclear

transport of the conjugate as it limits the distribution of the sensitizer from locating in photosensitive sites. Adenoviruses aptly break open endosomes upon infection and therefore it was postulated that the bioconjugates would target the nucleus much more quickly and efficiently in the presence of adenoviruses. This indeed proved true. Rosenkranz and Sobolev have written comprehensive reviews on this subject (Rosenkranz et al., 2000; Sobolev et al., 2000).

Adenoviruses have yet another potential role in photodynamic therapy, that of a gene therapy vector. A yeast vector system for manipulating the adenoviral genome has been developed and used to construct a virus expressing a mutant form of ALA-synthase (Gagnebin et al., 1999). This mutated enzyme lacks the iron response element which regulates its translation and import to the mitochondria. This lead to the accumulation of endogenous photosensitizers in infected cells, conferring photosensitivity. Unlike conventional PDT this viral approach restricts photosensitivity by biological rather than purely physical or chemical means thus improving targeting.

6.7 Advances toward peptidic carriers

Small peptides are readily prepared by automated solid phase peptide synthesis. The several possible combinations of natural and non-natural amino acid sequences make this a versatile class of molecules. In addition peptidic vectors are desirable as they invoke minimal humoral and sytemic immune responses. The RGD motif binds with high affinity to several of the integrin class of cell surface receptors. As discussed in chapter 5, RGD peptides have several therapeutic applications. One such application was as a stimulator of apoptosis, in particular of endothelial cells of angiogenic vessels (Brooks et al., 1994). A second potential use is as a carrier for chemotherapeutic agents

such as doxorubicin (Arap et al., 1998). In the hopes of developing either a peptidic carrier system for phthalocyanines or an adjunct therapy to PDT, chapter 5 details a study of an RGD containing peptide used in conjunction with $AlPc_{S2adj}$ PDT. It was found that a soluble RGD peptide attenuated PDT induced apoptosis. Generally, a soluble RGD peptide, when in contact with adherent cells disrupts the extracellular matrix thus blocking integrin signaling to the ECM and stimulates apoptosis. Buckley proposed an alternative method, that soluble RGD causes apoptosis via directly binding to and activating procaspase 3 (Buckley et al., 1999). At higher concentrations (10 mM) of the RGD peptide, we observed apoptosis with both a receptor positive and a receptor negative cell line therefore suggesting no involvement of the integrin receptor. At slightly inferior concentrations, there was a protection against PDT induce apoptosis in both cell lines with a much more pronounced protection in the receptor positive A549 cells. Not to completely rule out integrin receptor involvement, Whitlock and associates found that $\alpha_M\beta_2$ integrin signaling could either enhance or inhibit apoptosis of neutrophils depending on the proapoptotic stimuli (Whitlock et al., 2000). Activation of this class of integrins accelerated apoptosis induced by UV irradiation, Fas ligation and TNFα. However, integrin clustering without activation, resulted in inhibition of apoptosis.

In the current study, quenching of the reactive oxygen species by the peptide was ruled out as several different experimental parameters were changed to physically remove the peptide prior to PDT. The protective effect was still apparent and significant in the A549 cells whereas in the receptor negative cell line, EMT-6, the protection against apoptosis was almost abrogated. It was proposed that the RGD peptide, when rinsed, was

readily released from the EMT-6 cells, thus diminishing the protective effects whereas in the A549 cells, the peptide release was less. Studies using a radiolabeled peptide could prove useful in this capacity to determine peptide movement across the different cell membranes.

The A549 cells were previously shown in chapter 4 to bind with high affinity the radiolabeled RGD peptide whereas no significant binding was apparent in the EMT-6 cells. It is interesting that RGD has the most effect on A549 apoptosis. It could be possible that two different mechanisms are involved in the protective effect depending on the cell line. A549 cells, when incubated overnight with RGD prior to Pc-PDT, had enhanced cell survival whereas the EMT-6 had none. Perhaps, a receptor mediated, albeit a low affinity binding receptor, plays a role in the A549 protection whereas, simple diffusion of the peptide across the EMT-6 membrane may account for enhanced EMT-6 cell survival under certain circumstances. In the former, perhaps there is increased anti-apoptotic protein expression required to decrease cell death, whereas in the latter, perhaps the RGD is able to get into the cell and physically disrupt the apoptotic cascade.

Studies involving an immobilized RGD peptide could help elucidate whether cell penetration is required to abrogate apoptosis. In addition, it was postulated that increased expression of anti-oxidants such as superoxide dismutase, glutathione peroxidase and catalase may be a result of RGD stimulated integrin signaling (Qin et al., 2001). Clustering and activation of integrin receptors promotes *de novo* protein synthesis which was an absolute requirement to promote the survival effect of the extracellular matrix (Bozzo et al., 1997). Hence, growing cells on RGD coated plates, prior to PDT, may help to determine whether integrin signaling is involved in cell survival under these

circumstances. Analysis of protein levels could prove invaluable in elucidating the signals involved in RGD protection from PDT induce apoptosis.

6.8 Conclusion

Since its fortuitous beginning a century ago, photodynamic therapy has grown exponentially into a useful therapy for a number of conditions. The clinical acceptance of Photofrin®, methylene blue, Visudyne™ and the prodrug ALA clearly shows the extreme promise of PDT as a treatment for both malignant and non-malignant conditions for which there are few other useful therapies. There are a number of second generation photosensitizers in the pipeline with superior photophysical and biological properties. The choice of vehicles and carriers has dramatic effects on the properties of these photosensitizers. Clearly the investigation and development of new vehicles and 3rd generation photosensitizers could allow PDT to reach its full potential. There remains a long list of potential vehicles and carriers for photosensitizers including growth factors, hormones, steroid analogs, signaling molecules, peptides, antibody fragments, viral components, oligonucleotides and other tumor and tissue specific compounds.

The current study confirms that phthalocyanines are potent photosensitizers that are readily substituted, yielding better uptake and photodynamically active agents. Monosubstitution of $AlPcS_4$ with carbon chains of varying lengths increases the efficacy of this photosensitizer both *in vitro* and *in vivo*. L-Tryptophan oxidation following irradiation surpassed that of the parental $AlPcS_4$ molecule when the lipophilic sensitizers were monomerized in 1 % CRM. Cell adsorption as well as photocytotoxicity using the A549 cell line varied directly with the degree of hydrophobicity: C16 > C12 > C8 > C4. A549 cells took up 7 times more $AlPcS_4$(C16) as compared to $AlPcS_4$(C4) after a 48 hour

incubation. Human LDL at 4 μg/mL decreased cell uptake of the Pc derivatives but had little or no affect on the cytotoxicity of the sensitizer presumably due to better subcellular localization. These lipophilic phthalocyanines were potent sensitizers *in vivo* using the EMT-6 tumor model. Complete tumor regression was obtained at doses as low as 0.2 μmol kg^{-1} using both the C12 and the C16 derivatives whereas $AlPcS_4$ was inactive at doses 25 times greater.

Protein carriers such as lipoproteins enhance targeting of the sensitizer to cancer cells which can overexpress the LDL receptor (Gueddari et al., 1993). Attachment of $AlPcS_4$ via covalent coupling to the apolipoprotein through a caproic acid spacer chain or via non-covalent adsorption of $AlPcS_4$(C12) in the phospholipid part of the LDL was used to further determine the utility of LDL as a sensitizer transporter. The $AlPcS_4A_2$-LDL bioconjugate was only slightly phototoxic *in vitro* with LD_{90} values of 27 and 33 J cm^{-2} against the EMT-6 and A549 cell lines, respectively. LD_{90} values of 2 and 4 J cm^{-2} were measured for the non-covalently labeled $AlPcS_4$(C12)-LDL conjugate using identical experimental conditions. Clearly, LDL-association with lipophilic phthalocyanines via adsorption into its phospholipid bilayer augments the *in vitro* phototoxicity of the Pc. However, *in vivo*, the EMT-6 tumor response of the free $AlPcS_4$(C12) is similar to that of the LDL-associated dye, most likely due to the known redistribution of amphiphilic photosensitizers to serum lipoproteins upon injection.

Adenovirus proteins were studied as potential Pc carriers. $AlPcS_4$ was covalently coupled to various adenovirus type 2 capsid proteins, including the hexon, penton base and fiber, via one or two caproic acid spacer chains in 7:1 to 66:1 molar ratios. Adenoviruses gain access to cells via receptor-mediated endocytosis. Adenoviruses

attach to cells via the fiber capsid protein/receptor interaction while cell internalization involves binding of the virus to α_v integrins, a process mediated by RGD sequences found in the penton base of the adenoviral capsid. Cell adsorption studies were carried out on the integrin receptor positive A549 cell line. All Pc bioconjugates exhibited significantly improved cell uptake as compared to free Pc derivatives. In the meanwhile, the photocytotoxicity of the bioconjugates was determined against integrin receptor positive A549 and HEp2 and receptor negative EMT-6 cells. The Pc bioconjugates showed improved activity compared to the parent compounds in the receptor positive cell lines. Pcs labeled with the RGD-containing penton base were most phototoxic requiring roughly half the light dose to induce 50% cell kill as compared to the unlabeled compound. Complete tumor regression of EMT-6 tumors implanted on Balb-c mice was obtained using a mixture of adenovirus type 2 soluble proteins convalently labeled with $AlPcS_4A_2$ at a dose of 0.5 μmol kg^{-1} and 400 J cm^{-2}. Unlabeled $AlPcS_4A_2$ requires 1 μmol kg^{-1} at the same light dose. This suggests that the high affinity RGD/receptor complex is able to target phthalocyanines for PDT.

The effect of an RGD containing peptide on the photodynamic action of $AlPcS_{2adj}$ was studied *in vitro* using both a receptor negative and a receptor positive cell line, EMT-6 and A549 cells, respectively. At elevated RGD concentrations, ≥10 mM, RGD induced apoptosis. However at lower concentrations, the RGD abrogated the apoptotic effect of PDT in both cell lines, the effect being more pronounced in the A549 cells. At an RGD concentration of 50 μM, there was over 75 % A549 cell survival following $AlPcS_{2adj}$ PDT. Only 30 % survival was observed when no RGD peptide was administered. The protection is seemingly independent of the integrin receptor because it is observed in the

receptor negative cells and the concentrations required are higher than those needed to saturate the receptor.

Further studies are warranted to elucidate the signaling properties of the RGD peptide. Only when we fully understand its role in apoptosis can we strategize to improve current PDT protocols. However, this work has clearly helped phthalocyanines along the road towards the fulfillment of their immense promise as photosensitizers for PDT.

Chapter 7.

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Chapter 8.

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Appendix 1.

Role of Activated Oxygen Species in Photodynamic Therapy

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Appendix 2.

Photodynamic Therapeutics: Basic Priniciples and clinical applications

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Appendix 3.

Current Status of Phthalocyanines in the Photodynamic Therapy of Cancer

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